the opinions of self-appointed medical advisors to political groups; nor even the profound thoughts that emanate from the mysterious recesses of the minds of economists. Just the considered judgment of America's representative medical men, whom a plain man might expect to know more about the practice of medicine than even a professor of sociology, or a doctor of law.

6. In whatever way the cost of medical service may be distributed, it should be paid for by the patient in accordance with his income status, and in a manner that is mutually satisfactory.

The voluntary plan offers a method by which this may be done; the compulsory plan makes employer and state contribute to the payment of these costs. The one offers a dignified, self-respecting method of self-help, compatible with our American way of life, while the other takes one more step toward the subjugation of the citizen by the state!

7. Medical service must have no connection with any cash benefit; the voluntary plan, of course, complies absolutely with this rule, but the compulsory plan flatly rejects it. It is curious, incidentally, that it does not seem to occur to the master minds who promote compulsory health insurance that if sickness disability benefits are needed they can easily be supplied by a simple amendment to the Unemployment Reserve Act, and that there is no need to tie them into a system of medical care.

The eighth and ninth rules are reasonably complied with by both plans of prepayment care, and need not be discussed here.

10. There should be no restrictions on treatment or prescribing not formulated and enforced by the organized medical profession. With compulsory health insurance administered by the governing authority—apparently the Unemployment Reserves Commission, through a politically appointed medical director and with the advice of an advisory board, consisting of two representatives of employers and three representatives of labor—the impossibility of even remotely approaching compliance with this dictum is apparent, while, under the voluntary method, compliance is complete.

IN CONCLUSION

Thus it would seem, assuming that we have stated principles correctly, and have reasoned logically, that social trends beyond our control are inexorably forcing us toward a change in the plan of administering medical care. If we are to discard, however unwillingly, the traditional fee-for-service basis of payment, we must substitute something for it. Our alternatives seem to be public or state medicine on the one hand, and periodic prepayment plans on the other. That all contain objectionable features cannot be denied, but our task is to choose that method containing the smallest number of such objections, and the one whose flexibility is such that we may hope to mold and shape it. The present high plane of medical practice is largely the result of constant supervision of that practice by organized societies of physicians. When professional control of the practice of medicine is destroyed, the result is an impersonal perfunctory service, and the only method we can now see which will prevent this disastrous result by retaining the necessary supervision is that of the voluntary prepayment plan. Its success, the high standards of medical care, and the satisfaction which you will feel with it, rest in your hands; you are the shapers of its destiny, and, since its destiny and yours are one, of our own.

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POLIOMYELITIC INFECTION: ITS BASIC NATURE*†

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It is very important that the practitioner should have as clear an idea of the nature of poliomyelitic infection as possible in order that he may properly interpret the clinical signs and symptoms, know what measures are useful in treatment, and know what can and what cannot be accomplished in the way of prevention. Poliomyelitis has long been the subject of confusing and conflicting opinions regarding such fundamental things as the nature of the infecting agent, the manner and route by which it enters the human body, the parts of the body which it infects, and the order in which they are infected. To make matters worse, it is clear today that certain concepts have been so positively propounded by past authorities that they have been learned and accepted by the medical profession as a whole. Unlearning them will require time.

FILTERABLE VIRUS

That poliomyelitis is caused by a filterable virus of extremely minute size may now be accepted as proved; and claims that it is due to streptococci or other visible bacteria can be definitely and finally discarded.

The virus has strongly and, perhaps, almost exclusively neurotropic properties. Its natural host is the nerve cell, and it has no known capacity for multiplication in any other type of tissue. It may survive for a time in the nasopharynx, tonsils and cervical lymph nodes, but it has not been recovered with certainty from any other tissues outside of the nervous system in human beings. Even within the central nervous system it shows certain preferences for some types of cells over others. So far, therefore, as present knowledge goes, it is incapable of setting up a generalized or systemic infection; nor does it form a toxin. This point is stressed because, as will be discussed later on, poliomyelitis is frequently referred to as a primary systemic infection with secondary nervous manifestations; which implies that it is blood-borne and reaches the central nervous system through the blood stream. Virus has never been recovered from human blood, and disappears with great rapidity from the blood stream in animals injected intravenously.

There is sound reason for believing that the virus of poliomyelitis, like some other neurotropic

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* From the Stanford University School of Medicine, San Francisco.

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† Lack of space prevented appearance in this issue of two additional articles in this symposium on Poliomyelitis. See also in this issue, on page 67.

viruses, travels through the axis cylinders of nerves; here and in the main body of the nerve cells it multiplies and progressively infects other nerve axons and cells. Thus, it tends to spread along nerve tracts, rather than along vascular or lymph channels. There is doubtless a considerable escape of virus into the supporting tissues of the central nervous system which sets up a defensive, inflammatory reaction, consisting of hyperemia, fluid exudate, and polymorphonuclear and microglial cells. Foci of such inflammatory reaction in the nervous tissue have been shown by Spielmeyer to be the earliest recognizable reaction in human poliomyelitis; antedating the perivascular and meningeal accumulations of lymphocytes, and the necrosis of nerve cells.

MODES OF ENTRANCE

Experimentally, it has been shown that the ways in which the virus can gain entrance into the body and produce infection are of two sorts. The first involves no damage to the body surfaces and, so far as we know, this can occur only at one place—the olfactory mucosa in the upper nasal passages, where nerve fibers lie free on the surface. Such an anatomical arrangement exists only at this place. Every breath that we inspire through the nose has the potentiality of depositing foreign matter on these nerve fibers. Experimentally, the disease can be produced with great regularity when virus is placed in the nasal passages; and that it follows the olfactory fibers, and no others en route to the brain, is proved by its failure to infect when the olfactory bulb is removed. Experimental poliomyelitis produced by the olfactory route is an accurate facsimile of the severer types of the human disease, particularly in the kind and distribution of pathologic lesions. Positive and conclusive proof of the nasal route of entry in man is, and probably always will be wanting, since it would demand a series of observations in persons without olfactory nerves or olfactory bulbs. It is, however, highly suggestive that outside of the central nervous system the only sources from which virus has been recovered in human beings are the nasopharynx or the structures intimately connected by lymph drainage with it—the tonsils and cervical nodes—and the stools, where obviously it may have come from swallowed nasopharyngeal secretions.

Another possible nontraumatic mode of entrance, and one much debated, is through the gastro-intestinal tract. Experimental work has thrown strong light on this problem. It should be pointed out that the rhesus monkey, which is so highly susceptible to poliomyelitis, has a gastro-intestinal tract very similar to that of man. In this animal, in properly conducted experiments, large amounts of highly virulent poliomyelitis virus have been shown repeatedly and regularly to pass through the intestine without causing infection, and to be recoverable in active form from the stools. This point has been amply and repeatedly proved by the careful researches of Clark, Preston and Roberts, and Flexner. Only when, as in simple feeding experiments, the virus has access to the nasopharynx, or when, as in Toomey's experiments, the gut is grossly traumatized, does infection by the gastro-intestinal route succeed. The fact that in the human disease the lower extremities are most often paralyzed has been used as an argument in favor of the gastro-intestinal route. The argument, however, fails, since in animals inoculated intracerebrally the same thing is true. The fact that virus is often found in the stools in cases of poliomyelitis is, therefore, no indication of gastro-intestinal infection. Indeed, Trask, who has perhaps succeeded more often than anyone else in recovering virus from stools, both in abortive and in paralytic poliomyelitis, believes that its origin is swallowed nasopharyngeal mucus. I suppose that the idea of a primary gastro-intestinal infection was first suggested by the frequent occurrence of so-called gastro-intestinal symptoms at the onset and during the disease, and that there is perhaps a certain superficial reasonableness in the suggestion. When the facts are examined more closely, however, it becomes clear that the only common symptoms of this sort are vomiting and constipation, diarrhea being quite exceptional. Vomiting in a disease which so conspicuously affects the central nervous system should certainly be considered as of nervous origin, particularly when lesions are so frequently found in those areas near the third ventricle and in the medulla, disturbances of which are commonly associated with vomiting. Constipation is certainly not evidence for an inflammatory, irritating lesion of the bowel. Indeed, as Müller has suggested, it may well, like the bladder retention which so often occurs at the same time, be of central origin. Clinical as well as experimental evidence, therefore, fails to supply any valid argument in favor of the gastro-intestinal route. One need hardly consider seriously the possibility that traumatizing, obstructive or ulcerative lesions of the gut play any etiologic rôle of importance.

OTHER INFECTION ROUTES

The second way in which poliomyelitis infection can be produced depends on traumatic interruption of the body surfaces, with introduction of virus through a penetrating lesion. Experimentally, animals can be infected by such a method, usually injection, almost anywhere: in the skin, into the eye, into peripheral nerves, into the wall of the intestine, into the peritoneum, into the subarachnoid spaces, and into the brain. Such trauma always involves bringing virus into contact with nerve fibers. Direct injection into the blood stream, it is interesting to note, is usually ineffective unless very large amounts of virus are used. Translating these results into possible ways of human infection, one might think of insect bites, abrasions of the skin, injections of incompletely neutralized virus for purposes of immunization, and introduction of virus incidental to operation on the nose and throat or gastro-intestinal tract in individuals who happened to be harboring virus in these areas. The possibility of insect vection has been considered for many years and, while it doubtless remains open, no direct evidence has been presented in its favor, and no particular insect has been implicated. Poliomyelitis from injections for purposes of immunization has apparently occurred a few times and has led to the abandonment of the procedure. The disease has a number of times followed adenotonsillectomy, and it is interesting, as an illustration of the characteristic way in which poliomyelitis infection follows nerve channels, that the paralysis in these cases is nearly always bulbar; the virus having clearly followed the cranial nerves supplying the traumatized pharynx up to the pons or medulla. No instances of poliomyelitis occurring after operations on other parts of the body have come to my attention. It is probably wise not to perform adenotonsillectomy during epidemics of poliomyelitis unless operation is urgent.

It is possible that virus might enter the body and produce poliomyelitis through skin abrasions and other superficial trauma. Experimentally, intradermal inoculations are often successful. There are, however, no data favoring such a route of entry in man.

COMMENT

Weighing the evidence now available, it seems fair to conclude that, in human poliomyelitis, infection enters the body in the great majority of cases not by trauma, not by way of the gastrointestinal tract, but by way of the nasal passages and, specifically, by way of the olfactory nerves—presumably from droplets or dust in which virus is present.

COURSE

The course of infection, after it has entered through the olfactory fibers, can be followed closely in the experimental animal, and there are good reasons for believing that in man it is the same or similar. Two to four days later virus can be found in the olfactory bulbs, but not further. A day or two later it is found in the brain stem, and shortly after that it is first found in the spinal cord. Along this descending pathway, lesions of varying severity can be found: but in general actual destruction of nerve cells is limited to the medulla and spinal cord. In man the distribution and nature of the lesions in cases studied early in the disease are strikingly similar to those in the monkey. The disease is emphatically *not* a simple myelitis; it is an encephalomyelitis. This fact was noted by the earliest observers of the human pathology—Harbitz and Scheel, Wickman, Müller, and others; but because of the accompanying perivascular and meningeal accumulations of small cells and the generalized hyperemia, they concluded that the primary insult was on the vessels and meninges, that the infecting agent first penetrated these structures and, at a later stage, infected the nerve tissue proper. It remained for later investigators, such as Hurst, Spielmeyer, and Környey, to show that the reverse is true; that the primary lesions are in the parenchyma of the central nervous system, and that the small-cell infiltrations and hyperemia along the vessels and in the meninges—which, by the way, are responsible for the characteristic alterations of the spinal fluid—are secondary. The concept of an infection attacking and penetrating the blood- brain or choroid- meningeal barrier, must definitely be abandoned, even though it be so ingrained in our thinking that many clinicians today still refer to the preparalytic phase as systemic or meningeal, and consider the abortive and nonparalytic cases as those in which infection has failed to pass the barrier; hoping, at least, that convalescent serum may prevent the barrier being passed and nerve tissue being infected. The plain fact is that poliomyelitis in every case—abortive, nonparalytic and paralytic alike—is an infection of the nervous tissues. The all-important questions are how far the infection will spread within the central nervous system, and whether the nerve cells will become so heavily infected that some or many of them will die: or, in clinical terms, whether the patient will become paralyzed or die.

It is entirely erroneous to assume that nerve cells infected with poliomyelitis virus necessarily die: in the majority of cases none of them, so far as we can tell, do; and in all but the fatal cases only a relatively small number of them succumb. For, while nerve-cell infection in the average case is extremely widespread, full recovery is the rule for all but a few of the affected elements, and these limited to but a few areas, especially in the spinal cord.

CLINICAL RELATIONSHIPS

The fact that poliomyelitic infection, from its beginning, is a parenchymal disease of the central nervous system necessitates a clinical reorientation. It is familiar to every clinician that at the onset there is a complex of symptoms, consisting of fever, vomiting, headache, drowsiness, malaise, general hyperesthesia, sweating, flushing, rapid pulse, ataxia, and so on, which may or may not be followed by paralysis. It has long been customary to regard this group of symptoms as due to general or "systemic" infection, and to consider that during this period the infection has not as yet reached the central nervous system. Since this belief is now untenable, we must seek another explanation for the early symptoms. Such an explanation lies near at hand and is based on the known pathologic changes in the brain stem. The close resemblance of the early stage of poliomyelitis to encephalitis was suggested over twenty years ago by Müller, and I have discussed the subject at some length in another place. We can, I believe, with considerable certainty ascribe the early symptoms to the encephalitis which earlier as well as later investigators (Spielmeyer, Stiefler and Schenk, Környey, and Peters) are unanimous in reporting during the earliest days of the disease. The lesions are slight in the cerebral cortex, but conspicuous in the hypothalamus, thalamus, midbrain and medulla, and correspond closely in distribution with those which I have found in the preparalytic period in the monkey after intranasal inoculation. The centers particularly involved are those (in the hypothalamic area) which control or affect the vegetative functions, temperature, sleep, the movements of the gastro-intestinal tract, vascular tone, sweat; also those (in the thalamus) which have to do with the affective state; that is, the general sense of well- or ill-being) as well as the general as opposed to the localized consciousness of sensory stimuli; and those (in the midbrain) which mediate the balance between antagonistic muscle groups through the cerebellar relay in the red nucleus. Involvement of the substantia reticularis (which runs from the hypothalamic area down to and through the medulla and has to do with autonomic functions) is particularly conspicuous. The symptoms at the onset of poliomyelitis are closely correlated with the regions thus found to be involved in the pathologic process, and the usual absence of cortical signs and symptoms—such as disturbances of consciousness, hemiplegias, paraplegias, and so on—corresponds with the slightness of the pathologic changes in the cerebral cortex.

The character of the changes in the cerebrospinal fluid, and the variability of the time at which they appear, are best explained by an inflammatory process which proceeds from within the central nervous system toward the meningeal surfaces, and sometimes fails to reach the latter. Thus, an increase in cells and globulin often precedes any suggestion of paralysis, and it is as often present in nonparalytic as in paralytic cases of the disease; on the other hand, it may be completely absent or minimal in cases with fully developed and extensive paralysis. There is, indeed, no true meningitis in poliomyelitis, but merely an outpouring here and there of globulin, of lymphocytes, polymorphonuclears and, occasionally, of microglial cells into the pial meshes and subarachnoid spaces from the perivascular channels that lead from the inner parts of the central nervous system to the meningeal surfaces. There is also a rather generalized hyperemia in the substance, as well as on the surfaces, which may be in part responsible for some of the signs and symptoms that simulate meningitis.

OTHER PATHOLOGIC CHANGES

We should consider briefly the pathologic changes which are found, rather inconstantly, outside the central nervous system and which have been regarded as evidence of systemic as opposed to nervous tissue involvement. Hyperplasia of lymphoid tissue is perhaps the most frequent of these changes. Clinically, it is inconspicuous and inconstant. And since poliomyelitis virus cannot be found in these tissues except in the cervical glands and tonsils, it cannot be supposed that lymphoid hyperplasia in general is due to the direct action of the infecting agent. It is, therefore, necessary to look for another cause. This, I believe, is readily found in the character of the lesions in the central nervous system where, after the very first stages of the disease, there is a marked and extensive perivascular and submeningeal accumulation of lymphocytes—certainly enough to require of the lymphogenic structures a considerable degree of proliferation. Secondly, there are occasional evidences—small hemorrhages in the stomach and elsewhere, cloudy swelling in liver and other tissues, and so on—which have been attributed to some undefined toxic effect. It must be remembered that death in poliomyelitis results in nearly all cases from respiratory paralysis; that is, from anoxemia, and it seems reasonable to ascribe the so-called toxic lesions to this simple factor.

Following the initial stage of encephalitis, the infection may follow one or two courses. It may spread downward with greater or less rapidity and severity to infect the spinal cord, or it may die out entirely, the patient recovering without any sign of paralysis or other residual effect. If it spreads down to the spinal cord, it attacks and irritates not only the motor, but also the sensory, and sometimes the sympathetic elements as well; indeed, the sensory and sympathetic involvement commonly precedes the motor. Presumably the posterior ganglia are also involved in most cases. The physical signs and symptoms corresponding with this rather diffuse involvement of the cord are of great importance, especially for diagnostic purposes, and include localized pains, localized hyperesthesia of the skin, localized sweating, pain on flexion of the neck and spine (the so-called spine sign), the positive Kernig sign with pain, and tremor. It is important for us to remember here that these signs do not precede involvement of the central nervous system, but are actually manifestations of it. Curiously enough, such signs are sometimes, though not often, present in cases which do not show later paralysis. Thus, again, there is evidence that infection even in the spinal cord does not necessarily result in destruction of nerve cells with residual paralysis. Finally, as is familiar to us all, the third stage in which early weakness or paralysis indicates loss of function of the anterior horn cells of the cord does not always lead to permanent paralysis.

We have, therefore, a picture of a virus disease which has two outstanding characteristics: first, it is highly specific for nervous tissue; second, it has a striking tendency to die out at any stage and to produce lesions from which the affected tissues can, and frequently do rapidly and spontaneously recover.

PRACTICAL INFERENCES

In the light of these considerations, certain important practical inferences should be drawn. First, it is quite fruitless to hope that an early diagnosis followed by any kind of early treatment can prevent infection from invading the central nervous system; infection is already there. Second, it is extremely difficult to evaluate the effects of treatment because of the strong tendency of the disease to end in recovery without residual paralysis, an event which occurs in about 75 per cent of recognizable cases of poliomyelitis, without specific treatment. Third, the only time to prevent poliomyelitis is before the virus has been deposited on the surfaces of the body.

Immunity to poliomyelitis is peculiar; in fact, it has been questioned whether an effective immunity is established by an attack of the disease, and whether the specific antibody found in the blood has any protective powers at all. Second, cases in the same individual have been noted a good many times, and Fischer and Stillerman have even estimated that the incidence of attacks of poliomyelitis in individuals who have had previous attacks is approximately the same as that in individuals in the same community who have not had previous attacks. Experimentally, it is well established that the specific serum fails to protect animals if it is given at any time, even very shortly after virus has been inoculated. Recently, Harmon and his associates found the specific antibody present in greater than average concentration in the blood of an adult patient before paralysis developed, while the blood of eight out of fourteen patients contained the specific antibody very early in the disease. Such therapeutic series as have been studied by the alternate case method—one given serum and another not—show no significant differences in the incidence of paralysis. Nevertheless, the hope that in individual cases the administration of serum might enhance the natural tendency of infection to recovery, and thus minimize or prevent paralysis, is a natural one to hold and, in man at least, cannot be wholly denied.

If, as seems to be probable, the natural route of entry of the virus is from the nasal mucosa through the olfactory nerves and to the brain, the most logical and, on experimental grounds, the most promising, method of prevention is to block these nerve channels before exposure has occurred, and to keep them blocked so long as the danger or exposure is great—a method which may be of practical value in man. This subject is to be discussed by Doctor Schultz, who has done so much of the basic work on it.†

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EXPERIMENTAL POLIOMYELITIS: SOME BASIC CONTRIBUTIONS TO OUR UNDERSTANDING OF THE HUMAN PROBLEM *

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It is established that poliomyelitis is caused by a filter-passing virus. The size of this virus has been measured and found to be close to ten millimicrons, a figure which places it among the smallest of this group of infectious agents. Since poliomyelitis is a virus disease, we may well afford to think and reason about it in terms of what we know today of the basic features of this group of infectious diseases. Viruses and virus diseases have been the subject of extensive investigation during the past two decades, and our knowledge regarding them has now advanced sufficiently that we may speak of properties which are peculiar to all viruses, and to the pathological, immunological, and clinical features which more or less underlie all of the diseases caused by them.

FILTER-PASSING VIRUSES AND BACTERIAL MICROBES

To begin with, we should dismiss any lingering conception we may still have that the essential difference between the filter-passing viruses and bacterial microbes is one of size only. Such a concept is erroneous, for although most filter-passing viruses are considerably smaller than bacteria, this is probably the least important of the differences which exist between these two general groups of infectious agents. A much more fundamental difference lies in the fact that in the viruses we have infectious agents which not only single out given species of plants and animals as hosts, but tend to single out and apparently actually invade certain types of cells within those hosts. They are to be regarded, therefore, as specific cell parasites rather than relatively promiscuous intercellular tissue parasites. As infectious agents they exhibit not only a marked specificity for certain cells within a particular host, but depend on these cells being in their living state. None of the more than a hundred known filter-passing viruses have been propagated outside of the body on lifeless media such as bacteria will usually grow on. Some have been cultivated in artificial cultures of animal tissues, or in intact embryonic tissues such as the chorioallantois of the developing chick; but while they tend to be less exacting in the presence of less differentiated embryonic tissue, some are highly exacting even under these conditions. The virus of poliomyelitis, for example, has apparently been definitely propagated only in cultures containing nervous tissue from the human embryo. Extranervous tissue from the same embryos, as well as nervous tissue from other animals—embryonic as well as adult—have failed to provide the pabulum necessary for its multiplication.

VIRUSES AND CELLS

The close relationship of viruses to cells may also be recognized in the histopathology of these diseases, and this largely by virtue of the fact that the primary effects of the virus tends to center in certain special groups of cells. Although these primary effects differ and may range from a rapid degeneration or necrosis (as in the case of the motor-nerve cells in poliomyelitis) to an abnormal stimulation of cell proliferation, such as is seen in certain transmissible tumors of lower animals, or consist of some combination of these, they apparently always involve particular cells of one kind or another. These may be connective tissue cells, epithelial cells, nerve cells, or cells of some other type. While inflammatory reactions are frequently observed, these are usually secondary in character. In many virus diseases the effect produced is frequently associated, and may even be largely limited to the production within those cells of characteristic inclusion bodies, located either in the cytoplasm or in the nucleus. The presence of these bodies naturally adds to the weight of evidence that the changes produced are the result of an actual invasion of the cell by the virus. Added to this may be a highly restricted distribution of the virus within the infected host.

STUDIES ON EXPERIMENTAL POLIOMYELITIS

With this introduction, I should like to review briefly certain contributions which studies on ex-

† Article by Doctor Schultz follows.

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